REMARKS

Claims 54-59 and 62-70 are pending. No claims have been canceled or amended herein. Thus, claims 54-59 and 62-70 will remain pending and under examination upon the entry of this Communication.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the March 17, 2004 Advisory Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

The present invention provides a method of cell or tissue transplantation which combines microencapsulation of the graft with administration of inhibitors specific for the interaction between the B7 receptor of antigen presenting cells and the CD28/CTLA4 receptor of T-cells. The result is improved survival of the graft over either method alone.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 54-57 and 62-70 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

In particular, the Examiner continues to allege that the claimed methods lack enablement for the use of "an agent which inhibits an immune system costimulation event mediated by a cell surface molecule selected from the group consisting of B7, CD28, or CTLA4," as recited in claim 54.

In response, applicants respectfully traverse for the reasons of record and for the additional reasons set forth below. For the record, applicants point out that the Examiner's rejection pertains only to claim 54 and its dependent claims, 55-57 and 62-69. The rejection should not apply to claim 70 because claim 70 does not recite an "agent."

The Examiner conceded at page 3 of the Advisory Action that specific examples of agents which can be used in the claimed methods were known in the art and are described in the specification. For example, anti-B7 monoclonal antibodies (Lenschow p. 790), B7Ig, CD28Ig, and CTLA4Ig (Linsely at col. 14, 17) were recognized in the art as agents that inhibit the T-cell costimulation event mediated through the B7, CD28, or CTLA4 receptors, respectively.

The Examiner does not object to applicants' assertion that the range of possible inhibitors which satisfy the instant claims is limited to those which inhibit the interaction of the B7 receptor with the CTLA4 receptor. Nevertheless, the Examiner maintains the rejection on the grounds that this "range of possible inhibitors is not limited, but [encompasses] a whole universe of inhibitors...[and] [a]pplicant has not taught how to make these molecules for use in the claimed method."

Thus, the Examiner concedes that there are art-recognized inhibitors that can be used in the claimed methods. However, the Examiner requires applicants' specification to teach how to *make* all possible inhibitors of the B7:CTLA4 receptor interaction in order to enable the claimed methods. Applicants maintain that the Examiner lacks any basis for imposing such a requirement under 35 U.S.C. §112, first paragraph. The test of enablement is whether "the experimentation needed to practice the invention [is] undue or unreasonable." M.P.E.P. §2164.01.

Specific technical reasons are required in order to support the Examiner's rejection based on lack of enablement. M.P.E.P. §2164.04. Yet, the Examiner has provided no specific technical reasons why one of skill could not carry out the claimed methods without undue experimentation using the materials taught in the specification and the art. Instead, the Examiner asserts that enablement requires applicants to teach all possible starting materials that could be used in the claimed methods. Contrary to the Examiner's assertion, "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. §2164.01(b). The Examiner does not dispute that the specification discloses at least one method of making and using the claimed invention which correlates with the entire scope of the claim. Instead, the Examiner rejects the claimed methods for lack of enablement because applicants have not taught how to make all possible inhibitors that could be used in the claimed methods. Applicants maintain that the Examiner's rejection on the stated grounds is without merit and respectfully request that the rejection be withdrawn.

In view of the above remarks, applicants maintain that claims 54-57 and 62-70 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 54-57 and 62-70 under 35 U.S.C. §103(a) as allegedly unpatentable over Lenschow in view of Goosen, Soon-Shiong, Akalin, Linsley, Padrid, and Steurer.

In response, applicants respectfully traverse.

Applicants maintain that the cited references fail to support a *prima facie* case of obviousness for the reasons of record and for the additional reasons set forth below.

The burden of proof is on the Examiner to establish a *prima facie* case of obviousness. Applicants note that "[a] reasonable expectation of success is the standard by which obviousness is determined." M.P.E.P. §2141. Applicants maintain that the Examiner has failed to meet the burden of establishing that there was either a motive to make the combination set forth in the methods of the instant claims or a reasonable expectation of success in improving graft survival via the claimed combination.

In particular, the Examiner has failed to demonstrate either a suggestion in the prior art to combine microencapsulation with an inhibitor of the B7:CTLA4 receptor interaction, or a reasonable expectation that this combination would improve the survival of microencapsulated grafts.

At page 6, the Examiner's formulation of the relevant art is that "graft rejection is due to infiltration of lymphocytes" (Lenschow) and microencapsulation prevents graft rejection "by protecting the transplanted cells from both cytotoxic T-lymphocytes and natural killer cells" and "immune system proteins" (Soon-Shiong and Goosen). The Examiner then asserts that "one would have expected that using microcapsules . . . certainly would be complementary to CTLA4Ig in protecting graft cells from cells of the immune system . . . and immune system proteins." This assertion does not follow from the Examiner's own formulation of the art. CTLA4Ig blocks a specific interaction between an APC and a host T-cell that is required for full T-cell activation (see Padrid, 1998, of record). According to the Examiner's own formulation of the

art, a microcapsule impermeable to cells and immune system proteins would block this interaction, making CTLA4Ig treatment *redundant*, and not complementary as the Examiner suggests.

Applicants maintain that Lenschow supports the formulation of the art which applicants have attributed to the Examiner and therefore teaches away from the claimed combination of microencapsulation with an inhibitor such as CTLA4Ig. In support of their position, applicants point to Lenschow (1992). Lenschow teaches that CTLA4Ig treatment prolongs graft survival in a model system which utilizes *human cells* transplanted into a mouse. At page 791 Lenschow teaches that the "results suggest that the immune response to the human islets involves direct presentation of *human* major histocompatibility complex-restricted islet antigens by *human APCs*." (emphasis added). Thus Lenschow teaches that CTLA4Ig prolongs graft survival by inhibiting the interaction between *mouse* T-cells which infiltrate the graft and *human* APCs which present the graft antigens. The Examiner acknowledges the teaching in the prior art that such a cell:cell interaction would be blocked by microencapsulation of the graft. Lenschow further suggests that his results were contrary to the prevailing view: "[t]his possibility contrasts with conclusions drawn in previous studies in which the predominant pathway for xenogeneic antigen presentation appeared to involve the processing and presentation of shed foreign proteins by syngeneic mouse APCs." Thus, the prevailing view was that *mouse* APCs presenting *shed* human antigens were the primary means of stimulating the mouse T-cell response. Again, the Examiner's own reading of the prior art acknowledges the expectation that this process would also be blocked by microencapsulation, since the capsule was impermeable to

immune system *proteins* as well as to cells. Thus, applicants maintain that the art teaches away from making the claimed combination because the art provides no reasonable expectation that combining CTLA4Ig treatment with encapsulation would improve graft survival over encapsulation alone.

None of the remaining references, when combined with Lenschow Soon-Shiong, and Goosen, overcome this deficiency of motive and expectation of success in combining CTLA4Ig (or other blocker of the B7+APC-dependent activation of T-helper cells) with microencapulation to enhance graft survival. The remaining references all teach the effectiveness of CTLA4Ig in inhibiting cell-mediated graft rejection, but none suggest combining CTLA4Ig with microencapsulation.

To the contrary, another study published by Soon-Shiong two years after the Soon-Shiong reference cited by the Examiner also teaches away from the claimed combination (Soon-Shiong, 1992, see applicants' July 27, 1998 Information Disclosure Statement). At page 773, Soon-Shiong summarizes the 1992 results. "This study demonstrates for the first time the efficacy of microencapsulated islet allografts in reversing spontaneous diabetes in the large animal model...The role of CsA [cyclosporin A] and the need for cytokine inhibition remain unclear; studies are ongoing to compare microencapsulated islet allografts with and without this dose of CsA." Soon-Shiong combined CsA treatment with microencapsulation based on the theory that inhibiting IL-1 and TNF production by host immune cells would improve the survival of the encapsulated graft. At page 774 Soon-Shiong discusses the knowledge in the art regarding graft failure and suggests further avenues of research, none of which is the claimed combination. "Several possible mechanisms regarding

long-term graft failure require ongoing exploration. These include examination of long-term viability of the nonvascularized islet, assessment of the natural life span of islets, and evaluation of the long-term mechanical integrity of the capsule membrane." Soon-Shiong further elaborates on ways to improve the mechanical integrity of the capsule memberane. Thus, despite discussing a number of other areas for further research, Soon-Shiong does not suggest combining microencapsulation with inhibition of the B7:CTLA4 receptor interaction. Instead, Soon-Shiong suggests other, entirely different avenues of research, specifically optimization of cyclosporin dosages to inhibit the cytokines IL-1 and TNF (see pg. 769, 773) and improvements in microcapsule design (p. 769, 773). Thus, applicants maintain that the prior art teaches away from the claimed combination.

In view of the above remarks, applicants maintain that the claims satisfy the requirements of 35. U.S.C. §103.

Summary

In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed fee, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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